

Polymorphous Low-Grade Adenocarcinoma

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Abstract: Polymorphous low-grade adenocarcinomas are minor salivary gland neoplasms with a predilection for intraoral sites. Women are affected twice as frequently as men, and generally present in the fifth to sixth decade of life with a painless intraoral mass. The palatal mass is, on average, about 2 cm in greatest dimension. The tumors are submucosal, identified below an intact mucosa as a well-circumscribed although unencapsulated mass. The tumor is characterized by a polymorphous growth pattern, with individual tumors demonstrating multiple patterns, including solid, ductal-tubular, cribriform, trabecular, and single-file growth. Neurotropism is common, frequently forming a central nidus around which a “targetoid” pattern is formed. The neoplastic cells are isomorphic, containing round to oval vesicular nuclei with small nucleoli. Mitotic activity and necrosis are inconspicuous. There is frequently a slate gray-blue stroma separating the tumor cells. Immunohistochemical analysis demonstrates reactivity with cytokeratin, vimentin, S-100 protein, CD117, glial fibrillary acidic protein, and actin. Bcl-2 is overexpressed and there is generally a low proliferation index as determined by Ki-67 reactions. The tumor must be separated from pleomorphic adenoma (benign mixed tumor) and adenoid cystic carcinoma. Complete surgical excision will yield a more than 95% 10-year survival, although persistence or recurrence can emerge often in about 10% of patients more than 10 years later.

Key Words: polymorphous low-grade adenocarcinoma, pathology, clinical, prognosis, immunohistochemistry, differential, adenoid cystic carcinoma

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CASE REPORT

A 51-year-old woman complained to her dentist that she felt her dentures no longer fit. On performing an oral examination, the dentist identified a small nodular protrusion on the palate. It was slightly erythematous with an irregular

border. It was firm to palpation. A visit was scheduled 3 weeks later to fit the dentures. At follow-up, the mass “seemed” larger to the dentist, who scheduled an open biopsy with an oral surgeon. Before performing the biopsy, CT showed a mass in the soft tissues of the palate with an ill-defined border. There were no other systemic signs or symptoms.

A 1.8-cm mass was removed. The intact surface overlaid an infiltrative tumor arranged in a variety of different patterns of growth. The cells were small to medium, with round to oval nuclei and vesicular nuclear chromatin distribution. Nucleoli were inconspicuous and mitotic figures were absent. There was a matrix material separating the tumor islands that varied from eosinophilic to blue-gray. Immunophenotypic analysis showed keratin and S-100 protein immunoreactivity.

DISCUSSION

Polymorphous low-grade adenocarcinoma (PLGA) is a distinctive salivary gland neoplasm with a propensity to arise almost exclusively from minor salivary glands. It is associated with a slow growth and indolent biology. Previously used terms for PLGA include lobular carcinoma and terminal duct carcinoma.^{1,2} Although the frequency of this tumor is unknown, our awareness of PLGA as a distinct tumor has increased with the establishment of specific histopathologic criteria characterizing the tumor, and has made it the second most common intraoral malignant salivary gland tumor, accounting for about 2% of all salivary gland tumors.^{3–13} The differential diagnosis with adenoid cystic carcinoma, basal cell adenoma, and other salivary gland tumors is important because it does have an overall excellent prognosis.

Clinical Features

PLGA occurs over a wide age range (16–95 years; mean, 60 years), but does not seem to occur in the first or second decades of life. There is a nearly 2:1 female-to-male ratio. The typical clinical presentation of PLGA is that of a nonspecific painless mass located within the oral cavity, and the palate specifically. Patients may complain of their “dentures not fitting,” whereas many of these lesions are discovered incidentally during routine dental examination. When symptomatic, the duration ranges from a few days to 40

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years, with an average of about 2 years. Patients who present with pain, bleeding, or ulceration do not seem to have more aggressive disease, nor are they more prone to develop recurrences. Lesions that are more easily accessible tend to have a slightly shorter duration of symptoms.³⁻¹³

Pathologic Features

Macroscopic Findings

The tumors involve only minor salivary gland sites, most within the oral cavity. A few reports have suggested major salivary gland location, but they are not well documented. The tumors usually occur in the palate (about two thirds), with the lip, buccal mucosa, alveolar ridge, and base of tongue comprising the remaining cases. The tumors range in size from 0.4 to 6 cm in greatest dimension (average, 2 cm). Tumors of the lip are usually smaller, probably related to the ease of clinical visualization of a tumor of the lip versus one in the palate (rather than a difference in the overall biology of the tumor). Macroscopically, they are firm to solid ovoid masses, typically lying in close proximity to the overlying surface epithelium, and they are characteristically unencapsulated, although well circumscribed. Surface ulceration is not common. The cut surface is light-yellow to tan, without a specific gross appearance.^{1,2,4,5,14-16}

Microscopic Findings

PLGA is a malignant epithelial tumor characterized by infiltrative growth, morphologic diversity, and cytologic uniformity. The histology of PLGA comprises its infiltrative growth, patterns of growth, cytologic features, and the presence of matrix material. Characteristically, PLGAs are well circumscribed, but are not encapsulated tumors (Fig. 1). They

are seen to infiltrate into perisalivary gland adipose connective tissue, but true skeletal muscle invasion is uncommon. When present, skeletal muscle involvement usually presents as a compression of the muscle fibers. Infiltration into the adjacent salivary gland is quite common, however. Tumor cells invade and separate the lobular units of the residual minor salivary gland parenchyma, as well as wrap around the acini, but usually do not invade individual acini or duct structures (Fig. 2). Intact, normal acini and ducts can often be identified completely surrounded by tumor (Fig. 3). This may occur in the center of the neoplasm, but is more commonly seen at the periphery of PLGA. The surface epithelium is usually intact, but on occasion is ulcerated. When intact, the surface epithelium is usually uninvolved by tumor (Fig. 1).

PLGA may display a striking mixture of growth patterns within a single tumor (Fig. 4), including solid lobules, glandular profiles, tubules, trabeculae, cribriform nests, and linear, single cell "Indian-file" infiltration (Fig. 5). One or 2 cell layers of cuboidal to columnar cells line tubular areas. There are no differences in the cell types found in these 2 layers. Tumor cells are often arranged concentrically around a central nidus, creating a "targetoid" appearance. The nidus is often a small nerve bundle (neurotropism), and is quite characteristic for PLGA (Fig. 6). Papillary foci can be rarely seen, but when present represent only a minor component and are not the dominant pattern.

The tumor cells are uniformly round to polygonal, of small to medium size, with indistinct cellular borders and with abundant pale to eosinophilic cytoplasm (Fig. 7). The nuclei are particularly distinctive, being uniformly round to ovoid and containing open, vesicular nuclear chromatin and inconspicuous to small nucleoli (Fig. 8). Nuclear pleomor-

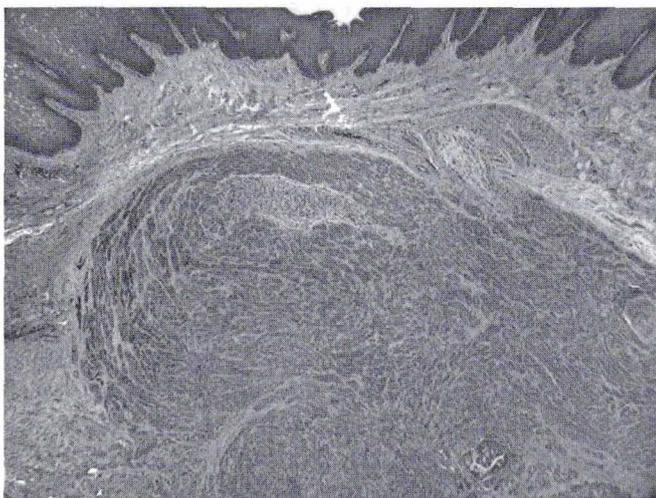


FIGURE 1. Low-power magnification of an intact surface epithelium and a well-circumscribed, although unencapsulated, mass.

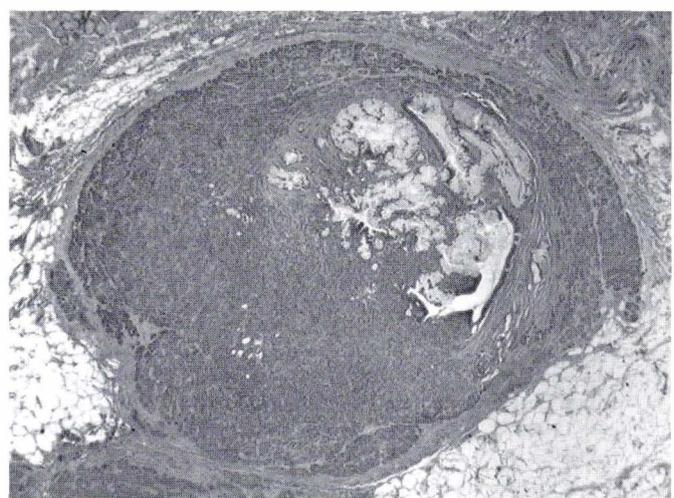


FIGURE 2. The tumor cells have encircled the minor salivary gland, but have not destroyed it.

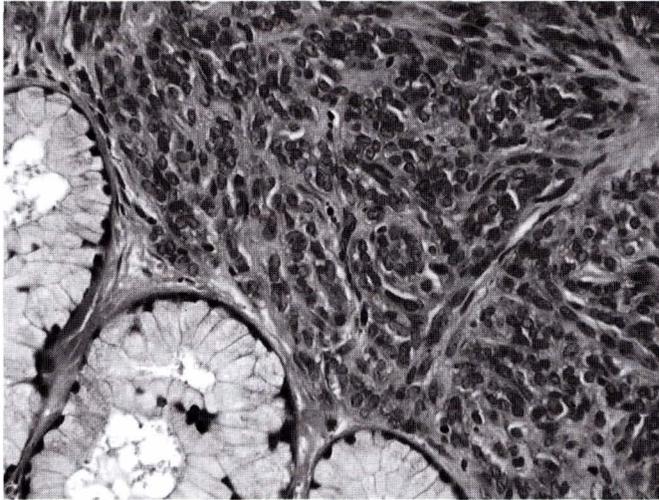


FIGURE 3. Intact, normal acini are surrounded by neoplastic cells.

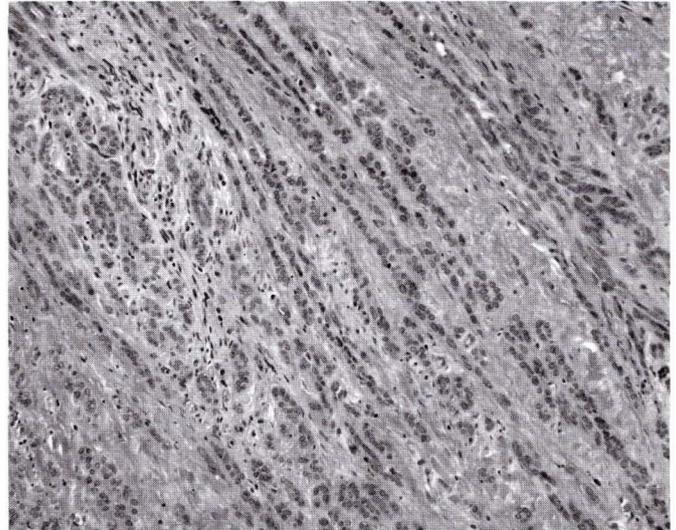


FIGURE 5. Single-cell, linear infiltration is noted and is most conspicuous at the periphery of the tumor.

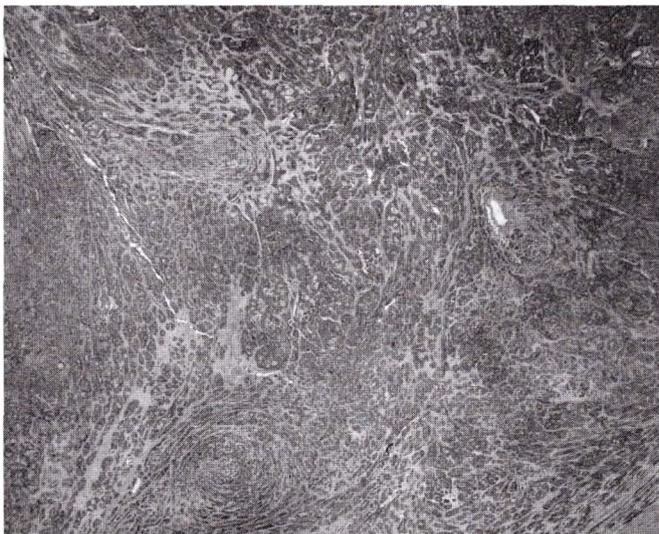


FIGURE 4. Variable architectures are seen within a single tumor, including cribriform, tubular, trabecular, and "targetoid."

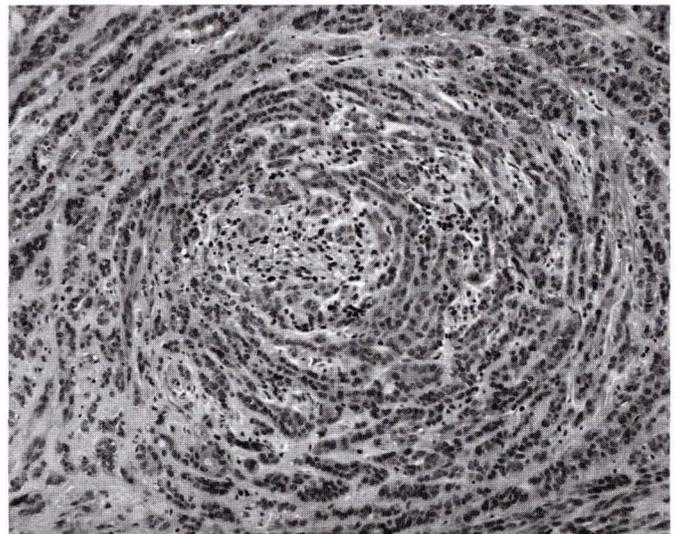


FIGURE 6. A "targetoid" appearance is created by a concentric ringlike distribution of the neoplastic cells, usually centered on a nerve.

phism is negligible, and mitotic figures are occasionally present, generally inconspicuous, and never numerous. Metaplastic changes, including squamous, sebaceous, or oncocytic alteration, are only rarely identified. Luminal crystalloids are not typical.

The tumor cells are surrounded by a hyalinized, slightly eosinophilic stroma that occasionally displays myxoid degeneration (Figs. 5 and 7). However, a characteristic slate gray-blue stroma is frequently encountered (Fig. 9). When identified, this background stroma is characteristic for PLGA, but can mimic the mucoid–myxoid matrix of pleomorphic adenoma.^{3–13,17}

Special Studies

Given that PLGA demonstrates a wide variety of growth patterns, the application of immunohistochemical studies to assist further in the differential diagnosis of the tumor can be performed, although with variable results. In general, the tumor cells are immunoreactive with cytokeratin, vimentin, S-100 protein, glial fibrillary acidic protein (GFAP), actin, and CEA, although the percentage of reactive cells and the intensity of the reactivity vary by case and within a case. Bcl-2 overexpression is common. The findings

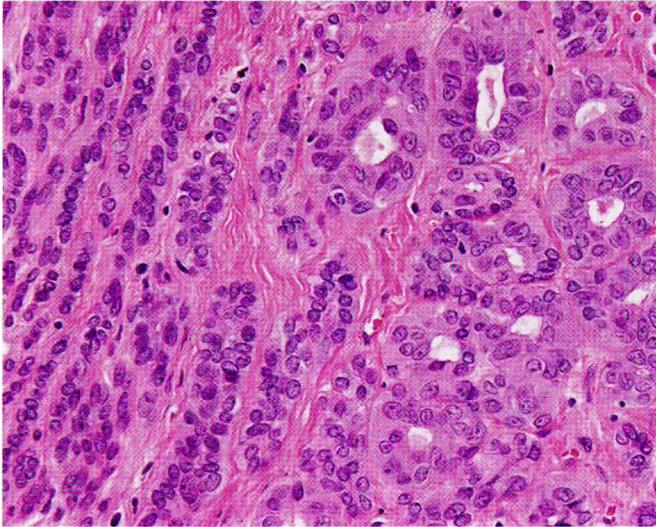


FIGURE 7. Strands of connective tissue separate the infiltrative and tubular-glandular tumor nests. The cells have ample cytoplasm and have even chromatin distribution.

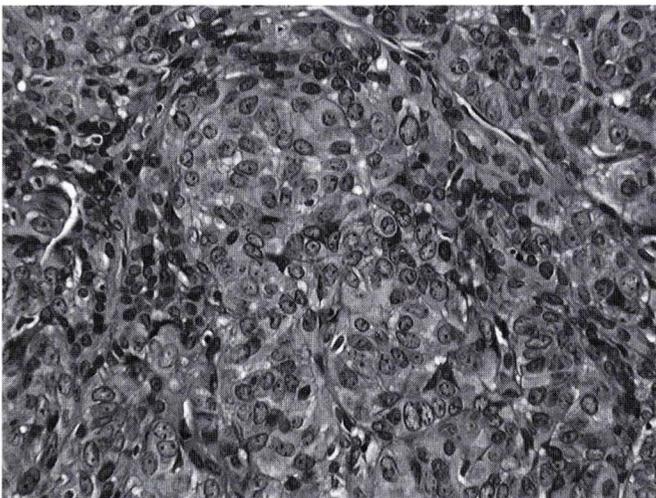


FIGURE 8. Round to oval nuclei have vesicular, open nuclear chromatin with small but distinctive nucleoli. Pleomorphism and mitotic figures are inconspicuous.

of GFAP, S-100 protein, and smooth muscle actin immunoreactivity can lend support to the diagnosis of PLGA, but are not specific, because these markers are frequently identified in other salivary gland neoplasms, particularly in benign mixed tumor (pleomorphic adenoma). CD117 is expressed, but not to the intensity and degree seen in adenoid cystic carcinoma (ACC). Overall, there is relatively weak and infrequent staining with the proliferation markers p53 and Ki-67 (MIB1), supporting the hypothesis of a low overall proliferation index.^{4–8,10,17–20} Curiously, recent genetic studies have displayed chromosome 12 abnormalities, specifically

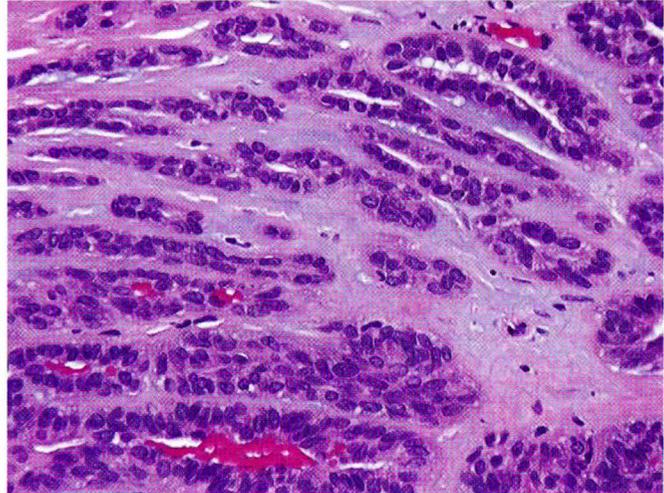


FIGURE 9. The characteristic slate gray-blue myxoid stroma separating small nests and tubules of neoplastic cells is noted.

affecting the 12q12-q13 region in both ACC and PLGA, suggesting there may be a common histogenesis.²¹

Differential Diagnosis

In general, the diagnosis of PLGA is not difficult. However, diagnostic difficulties due to histopathologic overlap may occur with mixed tumor (pleomorphic adenoma) and ACC. These diagnostic difficulties often occur during frozen section examination or when the biopsy is small. The cytomorphic features can be quite similar, thus rendering a definitive diagnosis of PLGA on a small biopsy virtually impossible at the time of frozen section. Furthermore, because mixed tumors of minor salivary glands are most often unencapsulated, differentiation from PLGA based on that feature is not reliable. The distinction between PLGA and pleomorphic adenoma can usually be made by identifying the presence of infiltrative growth, especially when combined with the presence of neurotropism. The typical plasmacytoid myoepithelial cells are seldom seen in PLGA.

ACC can mimic the growth patterns identified in PLGA, especially the proclivity for perineural invasion. However, in contrast with PLGA, the cells of ACC tend to be smaller with *hyperchromatic* nuclei, less cytoplasm, a higher nuclear-to-cytoplasmic ratio, and coarser nuclear chromatin. Differences in nuclear morphology are particularly striking and nearly pathognomonic. ACC lacks the slate-gray background matrix of PLGA. The immunohistochemical profile for ACC demonstrated positivity far above that of PLGA for Ki-67, p53 and bcl-2. Additionally, S-100 protein was found to be quite weak in ACC relative to PLGA, although CD117 tended to be strong in ACC.^{17,19}

Although limited foci of papillary growth can occur, no single tumor demonstrates a predominantly papillary pattern.

There can be focal areas of “degenerative” papillary formation, but this does not confer a specific pattern of growth. PLGA is not usually a cystic tumor and therefore it is unlikely to have “papillary projections.” Furthermore, the cytologic features in the foci of papillary growth are similar to the nonpapillary foci. A true papillary cystadenocarcinoma portends a more aggressive clinical course, with lymph node metastases and a higher frequency of local recurrence. This biologic behavior is distinctly contrary to that of PLGA.^{5,13,16–18,22}

Management

Complete surgical excision is the treatment of choice, although it is not uncommon to have an incisional biopsy as the initial diagnostic procedure. This procedure is usually followed by an excisional biopsy or a wide local excision. The extent of surgery may be larger than suggested by a low-grade neoplasm, but this is due to the frequent association with perineural invasion. Uncommonly, postoperative radiation therapy has been suggested for recalcitrant recurrences, but it appears to be palliative rather than curative. The overall survival for PLGA is generally excellent with conservative management, with more than 95% of patients alive after a mean follow-up of 10 years. Patients may die *with* disease, preceded by local recurrence, although they generally do not die *from* disease. Metastasis to the lung is most uncommon. Tumors localized to the hard palate are significantly more likely to be associated with tumor recurrence/persistence. Recurrence or persistence is present in about 10% of cases, emerging up to 14 years after initial presentation (mean, 7 years).⁵ In light of this prolonged latent period, diligent long-term patient follow-up is required. Women are more likely to develop recurrence than men. Size of the primary does not appear to influence disease progression or patient outcome.

CONCLUSION

PLGA is a distinctive salivary gland neoplasm arising almost exclusively in the oral cavity in patients in the middle decades of life. Patients are usually asymptomatic. The variable architecture, linear peripheral infiltration, perineural proclivity, and slate gray-blue background are characteristic. The cells are small to medium, with round to oval nuclei with open, vesicular nuclear chromatin and small nucleoli. Mitotic figures and necrosis are inconspicuous. Immunohistochemistry is not of particular value, but separation from pleomorphic adenoma and ACC are necessary to yield the excellent long-term clinical outcome achieved with conservative, but complete, surgical excision.

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